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ARTICLE

Exposure-safety and exposure-efficacy analyses for tisotumab vedotin for patients with locally advanced or metastatic solid tumors

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Abstract

The antibody-drug conjugate (ADC) tisotumab vedotin (TV) received accelerated approval from the US Food and Drug Administration for treatment of adults with recurrent or metastatic cervical cancer (r/mCC) with disease progression on or after chemotherapy. A population pharmacokinetic (PK) model, developed using dosing data from four clinical TV studies, was used to estimate individual exposure and explore safety and efficacy exposure-response (ER) relationships. Because PK analysis showed no appreciable accumulation of TV and monomethyl auristatin E (MMAE) with repeated dosing, cycle 1 exposure metrics and predicted average concentrations from time zero until end of the cycle in which an event occurred ($C_{avgLast}$) were used for ER analyses. The probability of achieving objective response increased significantly as the ADC cycle 1 maximum serum concentration (C_{max}) increased. The probability of treatment-related adverse events (AEs) leading to dose modification increased significantly as ADC cycle 1 area under the concentration-time curve (AUC) increased. Number of grade 2+ ocular AEs increased significantly as ADC cycle 1 AUC, C_{max}, and ADC $C_{avgLast}$ increased. MMAE cycle 1 AUC predicted risk of serious treatment-related AEs. The relationship between ADC exposure and efficacy end points suggests ADC treatment was associated with clinically meaningful response across the observed exposures; greater exposure was associated with increased efficacy. The relationship between ADC and MMAE exposure and safety end points suggests increased exposure was associated with increased AE risk. These results align with clinical findings showing TV 2 mg/kg (≤200 mg for patients ≥100 kg) every 3 weeks is efficacious and tolerable for patients with r/mCC.

Chaitali Passey, Jenna Voellinger, and Leonid Gibiansky contributed equally to this work.

ClinicalTrials.gov registration: This exposure-response analysis uses data from NCT02001623, NCT02552121, and NCT03438396.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

This is the first exposure-response (ER) analysis of tisotumab vedotin, an antibody-drug conjugate that has been approved in the United States for monotherapy in adult patients with recurrent/metastatic cervical cancer.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study used ER analyses to characterize the relationships of exposures to tisotumab vedotin and free monomethyl auristatin E with measures of efficacy and safety.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study provides new insight into the relationships among treatment exposure, efficacy, and safety end points.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The findings of the ER analyses support the efficacy and safety data, demonstrating that the recommended dose of tisotumab vedotin 2 mg/kg (up to 200 mg for patients ≥100 kg) once every 3 weeks provides a favorable balance between risk and benefit, with clinically important efficacy and an acceptable safety profile.

INTRODUCTION

Antibody-drug conjugates (ADCs), comprising an antibody, linker, and cytotoxic agent, have been successfully used for targeted delivery of cytotoxic compounds to greatly enhance their benefit–risk profile.[1–3] ADCs target a unique or preferentially distributed cell surface molecule on cells to deliver their cytotoxic payload. Tissue factor (TF), a transmembrane glycoprotein that functions in the blood coagulation cascade,[4] is expressed on the membrane of neoplastic cells and on tumor-associated endothelial and stromal cells, and its expression is associated with tumor growth, increased metastasis, and poor prognosis.[5–9] Aberrant overexpression of TF has been observed in various cancer types, including head and neck squamous cell carcinoma,[10] non–small cell lung cancer,[5,11] pancreatic cancer,[12] breast cancer,[13] and gynecologic cancers.[14–16]

Tisotumab vedotin (TV) is an investigational ADC that comprises a human TF-specific monoclonal immunoglobulin G1 antibody chemically conjugated via a protease-cleavable valine-citrulline linker to the microtubule-disrupting agent monomethyl auristatin E (MMAE). Cells expressing TF internalize TV upon binding, leading to the proteolytic cleavage of the linker and subsequent release of MMAE, killing target cells by direct cytotoxicity. In addition, TV may kill cells through bystander effects, antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis, and in a manner consistent with immunogenic cell death.[17–20]

Although TV has been investigated for the treatment of several solid tumors,[17,19,21] the most robust data exist for treatment in patients with recurrent/metastatic cervical cancer (r/mCC). In innovaTV 201 (NCT02001623), a phase I/II trial of TV monotherapy for the treatment of locally advanced or metastatic solid tumors known to express TF, a confirmed objective response rate (ORR) of 22% (95% confidence interval [CI], 12–35) was reported, as assessed by independent review of the expansion cohort of patients who had previously treated r/mCC ($N=55$).[22,23] This result was in accordance with the findings of the innovaTV 204 study (NCT03438396), in which a larger cohort of women who had r/mCC ($N=101$) were recruited, and a confirmed ORR of 24% (95% CI, 16–33) was assessed based on independent review,[20] leading to the accelerated approval by the US Food and Drug Administration of TV monotherapy 2 mg/kg (up to 200 mg for patients ≥100 kg) once every 3 weeks (q3w) for adults who have r/mCC with disease progression on or after chemotherapy.[24] The TV dose is capped at 200 mg in patients weighing greater than or equal to 100 kg to prevent adverse events (AEs). In the innovaTV 204 study, treatment-related AEs of special interest were ocular adverse reactions (53%; 2% grade 3), peripheral neuropathy (33%; 7% grade 3), and bleeding (39%; 2% grade 3); there were no grade 4 events.[20] Overall, findings from these trials have shown that TV monotherapy provides clinically meaningful and durable antitumor activity, with a tolerable safety profile in women who have previously treated r/mCC.

A population pharmacokinetic (PK) analysis was undertaken using data from four studies conducted to

evaluate TV in patients with cervical cancer and other solid tumors (innovaTV 201 [NCT02001623], innovaTV 202 [NCT02552121], innovaTV 204 [NCT03438396], and innovaTV 207 [NCT03485209]).[25] The developed population PK model and the actual dosing history were used to compute individual exposure estimates for each patient. We report the results of the exposure-response (ER) analyses between exposure and clinical response for multiple efficacy and safety end points using estimates of TV and unconjugated MMAE exposures from three of the studies (innovaTV 201, innovaTV 202, and innovaTV 204).

METHODS

Study design

The database for the exposure-safety analysis included data from 272 patients administered TV 2 mg/kg q3w in studies innovaTV 201 (expansion cohort), innovaTV 202 (expansion cohort), and innovaTV 204 (cutoff date February 6, 2020; Table S1). The database for the exposure-efficacy analysis included data from 101 patients from innovaTV 204 (cutoff date February 6, 2020). The innovaTV 201 and innovaTV 202 studies were phase I/II, dose-escalation and -expansion trials in patients who have locally advanced or metastatic solid tumors known to express TF. The innovaTV 204 study was a phase II open-label, single-arm, global trial of TV for patients with recurrent or extrapelvic metastatic cervical cancer who experienced disease progression on or after receiving a platinum-containing chemotherapy doublet in combination with bevacizumab (if applicable).

The ER analyses comprised exposure-safety and exposure-efficacy analyses. The exposure-safety end points were the probability of the following AEs: grade 2 or higher ocular AEs, grade 2 or higher peripheral neuropathy, grade 2 or higher bleeding AEs, treatment-related grade 3 or higher AEs, treatment-related dose modifications (dose reduction, dose interruption, and dose discontinuation), all serious AEs (SAEs), and treatment-related SAEs. Information on grading of AEs is shown in Appendix S1. The exposure-efficacy end points were ORR, progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Model-based evaluations of exposure versus safety end points were conducted using linear logistic regression (base model). An adjusted covariate analysis of safety (full model) was conducted using age, weight, sex, region (United States vs. Europe), tumor type, baseline tumor size, baseline albumin, baseline lactose dehydrogenase (LDH), renal impairment category (based on computed creatinine clearance category), hepatic impairment category (based on National Cancer Institute Organ Dysfunction Working Group classification for hepatic dysfunction), and baseline Eastern Cooperative Oncology Group (ECOG) performance status. Model-based evaluations of ORR were conducted using linear logistic regression (base model). An adjusted covariate analysis of ORR (full model) was conducted using age, weight, region (United States vs. Europe), baseline tumor size, baseline albumin, baseline LDH, renal impairment category, baseline ECOG performance status, baseline TF H-score, histology (squamous/not), previous bevacizumab treatment, and previous radiation therapy.

The population PK analysis showed no appreciable accumulation of ADC and MMAE with repeated dosing; therefore, cycle 1 (interval between the first and second doses) measures were used for all ER analyses.[25] Moreover, because the ADC trough concentrations were either near or below the quantification limit, they were not considered a useful measure of exposure. Exposure parameters in both the efficacy and the safety analyses included cycle 1 maximum concentration (C_{max1}), cycle 1 area under the concentration-time curve (AUC_1), and the predicted average concentration from time zero until the end of the cycle in which an event occurred using actual dosing history ($C_{avgLast}$) for ADC and MMAE, as well as cycle 1 trough concentration (C_{tr1}) for MMAE. For each safety or efficacy event, individual predicted average concentration from time zero to the end of cycle in which the event occurred was computed and used:

- Individual $C_{avgLast,ADC} = AUC_{ADC,Time}/Time$ for ADC
- Individual $C_{avgLast,MMAE} = AUC_{MMAE,Time}/Time$ for MMAE

where Time is the duration from the first dose to the end of the cycle in which the event or censoring (AE, PFS, or OS) was observed or the entire duration of treatment (for ORR and DOR analyses, and if the event or censor time was longer than the treatment duration). Duration of treatment in this case was defined as the time interval from the first dose until the last dose plus 21 days. The final model of the population PK analysis and the actual dosing history, which included dose delays, reductions, or interruptions, were used to compute the $C_{avgLast}$ exposure measures.[25]

Covariate definitions

All continuous demographic covariates were reported in International System of Units (SI units). SI and conventional units both, where applicable, were used for covariates of laboratory values. Details can be found in the population PK analysis report[25] and in Appendix S1: Tables S2 and S3.

TABLE 1 Summary of logistic regression models for AEs for ADC and MMAE.

AE	Exposure measure	Coefficient	SE	*p* Value	Model
Treatment-related SAEs	Cycle 1 AUC (MMAE)	0.008	0.004	0.033[a]	Base
		0.012	0.005	0.012[a]	Full
	Cycle 1 AUC (ADC)	0.013	0.012	0.287	Base
		0.005	0.015	0.721	Full
	Cycle 1 C_{max} (ADC)	0.037	0.019	0.048[a]	Base
		0.023	0.023	0.328	Full
	$C_{avgLast}$ (ADC)	0.212	0.271	0.433	Base
		0.059	0.304	0.846	Full
All SAEs	Cycle 1 AUC (MMAE)	0.011	0.004	0.002[a]	Base
		0.010	0.004	0.025[a]	Full
	Cycle 1 AUC (ADC)	0.000	0.010	0.960	Base
		0.004	0.012	0.745	Full
	Cycle 1 C_{max} (ADC)	0.003	0.015	0.824	Base
		0.009	0.019	0.635	Full
	$C_{avgLast}$ (ADC)	−0.105	0.213	0.622	Base
		−0.071	0.241	0.769	Full
Treatment-related grade 3+	Cycle 1 AUC (MMAE)	0.004	0.003	0.252	Base
		0.007	0.004	0.130	Full
	Cycle 1 AUC (ADC)	0.025	0.010	0.015[a]	Base
		0.017	0.013	0.192	Full
	Cycle 1 C_{max} (ADC)	0.057	0.017	0.001[a]	Base
		0.051	0.021	0.014[a]	Full
	$C_{avgLast}$ (ADC)	0.518	0.226	0.022[a]	Base
		0.324	0.253	0.200	Full
Treatment-related AE leading to dose interruption	Cycle 1 AUC (MMAE)	−0.009	0.006	0.164	Base
		−0.006	0.008	0.445	Full
	Cycle 1 AUC (ADC)	0.048	0.014	0.001[a]	Base
		0.038	0.017	0.026[a]	Full
	Cycle 1 C_{max} (ADC)	0.073	0.022	0.001[a]	Base
		0.071	0.028	0.010[a]	Full
	$C_{avgLast}$ (ADC)	0.630	0.319	0.048[a]	Base
		0.401	0.360	0.266	Full
Treatment-related AE leading to dose reductions	Cycle 1 AUC (MMAE)	−0.025	0.008	0.003[a]	Base
		−0.015	0.009	0.093	Full
	Cycle 1 AUC (ADC)	0.050	0.014	<0.0005[a]	Base
		0.046	0.017	0.006[a]	Full
	Cycle 1 C_{max} (ADC)	0.038	0.021	0.066	Base
		0.034	0.026	0.195	Full
	$C_{avgLast}$ (ADC)	0.552	0.298	0.064	Base
		0.159	0.340	0.640	Full

TABLE 1 (Continued)

AE	Exposure measure	Coefficient	SE	*p* Value	Model
Treatment-related AE leading to dose discontinuation	Cycle 1 AUC (MMAE)	−0.002	0.004	0.653	Base
		0.004	0.006	0.493	Full
	Cycle 1 AUC (ADC)	0.038	0.012	0.001[a]	Base
		0.032	0.015	0.037[a]	Full
	Cycle 1 C_{max}	0.059	0.019	0.002[a]	Base
		0.053	0.024	0.030[a]	Full
	$C_{avgLast}$ (ADC)	0.888	0.277	0.001[a]	Base
		0.777	0.323	0.016[a]	Full
Grade 2+ bleeding AEs	Cycle 1 AUC (MMAE)	0.007	0.005	0.105	Base
		0.003	0.006	0.644	Full
	Cycle 1 AUC (ADC)	0.007	0.017	0.659	Base
		0.014	0.020	0.474	Full
	Cycle 1 C_{max} (ADC)	−0.021	0.027	0.434	Base
		−0.014	0.032	0.658	Full
	$C_{avgLast}$ (ADC)	0.486	0.370	0.189	Base
		0.646	0.430	0.133	Full
Grade 2+ ocular AEs	Cycle 1 AUC (MMAE)	−0.026	0.006	<0.0005[a]	Base
		−0.024	0.006	<0.0005[a]	Full
	Cycle 1 AUC (ADC)	0.058	0.012	<0.0005[a]	Base
		0.064	0.014	<0.0005[a]	Full
	Cycle 1 C_{max} (ADC)	0.071	0.017	<0.0005[a]	Base
		0.079	0.021	<0.0005[a]	Full
	$C_{avgLast}$ (ADC)	1.191	0.245	<0.0005[a]	Base
		1.263	0.287	<0.0005[a]	Full
Grade 2+ peripheral neuropathy	Cycle 1 AUC (MMAE)	−0.012	0.005	0.032[a]	Base
		−0.009	0.007	0.162	Full
	Cycle 1 AUC (ADC)	0.017	0.012	0.153	Base
		−0.008	0.014	0.566	Full
	Cycle 1 C_{max} (ADC)	0.033	0.018	0.074	Base
		0.000	0.022	0.990	Full
	$C_{avgLast}$ (ADC)	0.231	0.265	0.383	Base
		−0.174	0.300	0.562	Full

Abbreviations: ADC, antibody-drug conjugate; AE, adverse event; AUC, area under the concentration-time curve; coefficient, exposure slope of the logistic regression model; $C_{avgLast}$, predicted average concentrations from time zero until end of the cycle in which an event occurred; C_{max}, maximum concentration; MMAE, monomethyl auristatin E; SAE, serious adverse event; SE, standard error.

[a]Analyses associated with $p < 0.05$.

Missing data imputation

Missing continuous covariates were imputed by the median value of the covariate within a study. The imputation flags (1 or 0) were provided for continuous covariates and for categorical covariates that were derived from the continuous covariates; any categorical covariates that could not be imputed were identified as a separate "Missing" category (for example, missing values for previous treatment category).

Software and models

The population PK analysis[25] used to compute exposures was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.4.3 (ICON Development Solutions). Computer resources included personal computers with Intel processors, Windows 10 Professional operating system (Microsoft), and Intel Visual Fortran Professional Compiler (version 11.0). All statistical and graphical analyses, including logistic regression,

Kaplan–Meier (KM) plots, Cox proportional hazard (CPH) modeling, and covariate analyses, were performed using R, version 4.0.2 for Windows (R project, http://www.r-project.org/). The function *glm()* with logit link was used for the logistic regression analysis. The functions *survfit()* and *coxph()* of the *survival* package were used, respectively, for KM plots and CPH modeling. Additional information can be found in the Appendix S1: Supplemental Text (S2–S4).

For each AE type, linear logistic regression models were implemented to assess the relationship between the probability of treatment-related AE occurrence and exposure (Appendix S1: Supplemental Text S2). The ORR was investigated using linear logistic regression models (Appendix S1: Supplemental Text S3). The following time-to-event (TTE) exposure-response relationships were investigated: PFS, OS, and DOR. Two analyses were performed for each survival measure. In the first analysis, patients were categorized by two equal-size exposure groups (defined by the median of $AUC_{1,ADC}$) and survival probability was illustrated using a KM plot for each of the exposure categories. In the second analysis, the exposure-survival relationships were described by semiparametric CPH models to evaluate the effect of exposure on survival and account for effects of prognostic factors (Appendix S1: Supplemental Text S4).

Ethics approval

All clinical studies were performed in accordance with good clinical practice guidelines from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and the principles of the Declaration of Helsinki. Protocols were approved by appropriate institutional review boards. Written informed consent was provided by all participants.

RESULTS

Exposure-safety analysis

The exposure-safety analysis was performed to evaluate safety data from 272 patients pooled from three studies (Appendix S1: Table S1). ADC exposure measures ($AUC_{1,ADC}$, $C_{max1,ADC}$, and $C_{avgLast,ADC}$) were strongly correlated to each other (correlation coefficient $r = 0.68$–0.84), as were MMAE exposure measures ($AUC_{1,MMAE}$, $C_{max1\,MMAE}$, and $C_{avgLast,MMAE}$; $r = 0.97$–0.98). There were no correlations between ADC and MMAE exposure measures ($r = -0.17$ to 0.15).

Both models showed that the probability of treatment-related AEs leading to dose interruption (full; $p = 0.026$), reduction (full; $p = 0.006$), or discontinuation (full; $p = 0.037$) significantly increased as ADC cycle 1 AUC increased (Table 1; Appendix S1: Figure S1A–C). Grade 2+ ocular AEs significantly increased as ADC cycle 1 AUC increased (full; $p < 0.0005$), ADC cycle 1 C_{max} (full; $p < 0.0005$), and ADC $C_{avgLast}$ (full; $p < 0.0005$; Table 1, Figure 1); subset analysis of innovaTV 204 data was consistent with the pooled data set (data not shown). The probability of AEs of grade

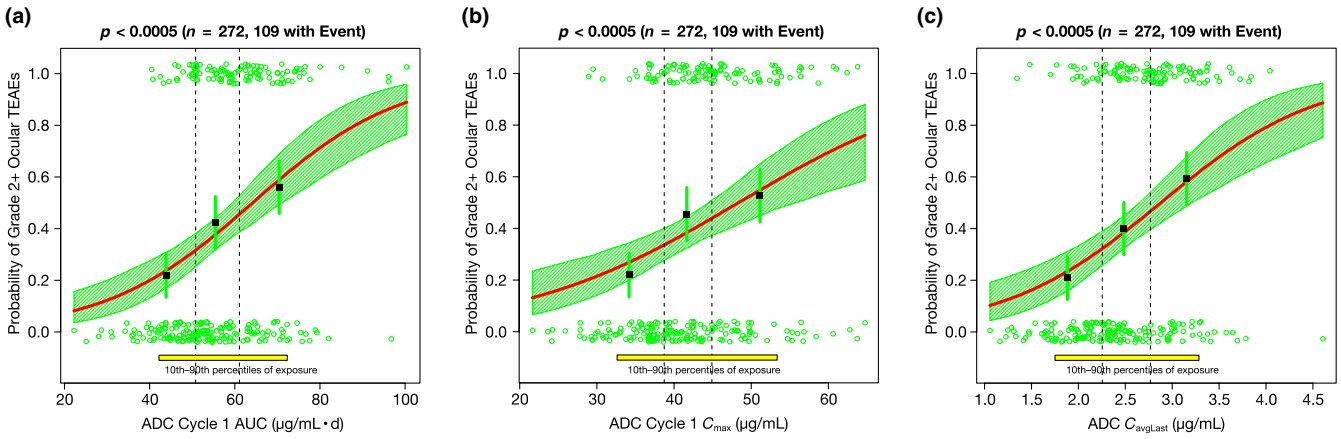

FIGURE 1 Logistic regression for grade 2+ ocular AEs versus ADC cycle 1 AUC, cycle 1 C_{max}, and $C_{avgLast}$ (base model). This figure shows the logistic regression for grade 2+ ocular AEs versus (a) ADC cycle 1 AUC, (b) ADC cycle 1 C_{max}, and (c) ADC $C_{avgLast}$ (base model). The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual patients who experienced events ($p = 1$) and those who did not experience events ($p = 0$) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of patients who experienced events in each exposure tertile and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure tertiles. The p value is provided by *glm()* function. ADC, antibody-drug conjugate; AE, adverse event; AUC, area under the concentration-time curve; C_{max}, maximum concentration; $C_{avgLast,}$ predicted average concentrations from time zero until end of the cycle in which an event occurred; TEAEs, treatment-emergent adverse events.

2+ bleeding and peripheral neuropathy was not correlated with ADC exposure (Table 1; Appendix S1: Figure S1D,E).

The probability of the occurrence of treatment-related SAEs (full; $p=0.012$) and all serious AEs (full; $p=0.025$) significantly increased as MMAE cycle 1 AUC increased (Table 1; Appendix S1: Figure S1F,G). The probability of the occurrence of grade 2+ ocular AEs was significantly inversely correlated with MMAE exposure (full; $p<0.0005$; Table 1).

Exposure-efficacy analysis

The exposure-efficacy analysis was done to evaluate efficacy data from 101 patients from innovaTV 204, in which all patients had cervical cancer (Appendix S1: Table S3). Most patients had squamous cell carcinoma (68.3%) and had undergone bevacizumab therapy (69.3%; Appendix S1: Table S3). ADC exposure measures ($AUC_{1,ADC}$, $C_{max1,ADC}$, and $C_{avgLast,ADC}$) were strongly correlated with each other (correlation coefficient $r=0.72$–0.89), as were MMAE exposure measures ($AUC_{1,MMAE}$, $C_{max1\,MMAE}$, and $C_{avgLast,MMAE}$; $r=0.95$–0.98). There were no correlations between ADC and MMAE exposure measures ($r=-0.13$ to 0.15).

The data set included 24 responders (23.8%), which was sufficient to investigate the effect of exposure on ORR. There was a higher percentage of responders among patients with higher ADC exposure, and a lower percentage among patients with higher MMAE exposure. For the base models, the probability of response significantly increased as ADC exposure increased (cycle 1 AUC and cycle 1 C_{max}) and significantly decreased as MMAE exposure decreased (cycle 1 AUC, cycle 1 C_{max}, and $C_{avgLast}$; Table 2; Figure 2). After accounting for the covariate effects, only the relationship with ADC cycle 1 C_{max} remained statistically significant (full; $p=0.005$).

The probability of a PFS event significantly increased as MMAE cycle 1 AUC, cycle 1 C_{max}, and $C_{avgLast}$ increased; however, after accounting for covariate effects, only the relationship between PFS and MMAE $C_{avgLast}$ was significant (full; $p=0.032$; Table 3). Both models showed that risk of death significantly decreased as ADC cycle 1 AUC (full; $p=0.010$) and cycle 1 C_{max} (full; $p=0.044$) increased and significantly increased as MMAE cycle 1 AUC (full; $p=0.001$), cycle 1 C_{max} (full; $p=0.001$), and $C_{avgLast}$ (full; $p=0.001$) increased (Table 3).

DOR was not correlated with ADC or MMAE exposure (Table 3). For all significant exposure-efficacy relationships, the relationship with MMAE exposure was opposite from the relationship with ADC exposure even though there were no strong correlations between ADC exposure measures and MMAE exposure measures.

TABLE 2 ORR: Summary of logistic regression models for ADC and MMAE.

Exposure	Coefficient	SE	*p* Value	Model
ADC cycle 1 AUC	0.032	0.016	0.048[a]	Base
	0.043	0.024	0.076	Full
ADC cycle 1 C_{max}	0.066	0.029	0.021[a]	Base
	0.146	0.052	0.005[a]	Full
ADC $C_{avgLast}$	0.068	0.389	0.861	Base
	0.262	0.498	0.598	Full
MMAE cycle 1 AUC	−0.027	0.013	0.031[a]	Base
	−0.026	0.018	0.139	Full
MMAE cycle 1 C_{max}	−0.236	0.109	0.031[a]	Base
	−0.212	0.151	0.161	Full
MMAE cycle 1 C_{tr}	−1.448	2.111	0.493	Base
	0.427	2.913	0.884	Full
MMAE $C_{avgLast}$	−0.790	0.310	0.011[a]	Base
	−0.632	0.410	0.123	Full

Note: A total of 8 baseline values for SUMDIAM were missing (6 patients from innovaTV 201; 1 from innovaTV 202; and 1 from innovaTV 204); data were imputed from the median values among patients with the same tumor type and non-missing SUMDIAM data.

Abbreviations: ADC, antibody-drug conjugate; AUC, area under the concentration-time curve; coefficient, exposure slope of the logistic regression model; $C_{avgLast}$, predicted average concentrations from time zero until end of the cycle in which an event occurred; C_{max}, maximum concentration; C_{tr}, trough concentration; MMAE, monomethyl auristatin E; ORR, objective response rate; SE, standard error; SUMDIAM, individual sum of tumor diameters at baseline.

[a]Analyses associated with $p<0.05$.

DISCUSSION

The US Food and Drug Administration–approved anticancer ADC therapies are based on the MMAE-linker payload technology, indicated by the name "vedotin."[20,24,26,27] The exposure-safety and exposure-efficacy relationships were explored for a range of exposures associated with TV 2 mg/kg q3w, a similar dosing regimen to the regimen used for other vedotin ADCs.[27–29] Regarding the safety outcomes, the probability of treatment-related AEs leading to dose modification significantly increased as ADC cycle 1 AUC increased, and the probability of grade 2+ ocular AEs occurring significantly increased as ADC cycle 1 AUC, ADC cycle 1 C_{max}, and ADC $C_{avgLast}$ increased (Table 1). Here, higher ADC exposure is associated with greater risk of ocular AEs, which might be related to TF expression in the ocular epithelium.[30,31] To this end, an eye care plan based on clinical trial experience has been developed[32] and continues to evolve as experience with TV grows.[20] The education of patients and provider teams is essential

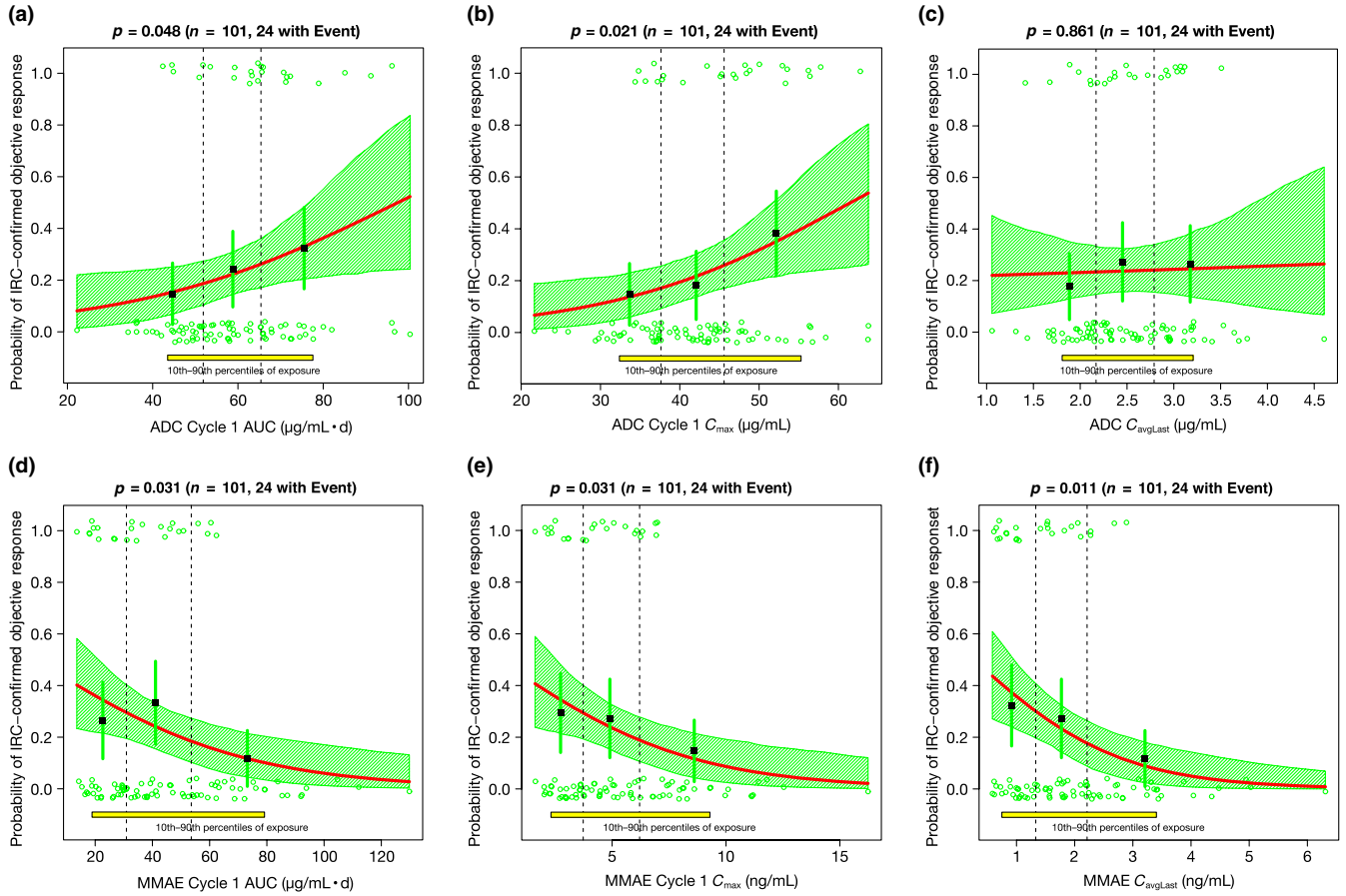

FIGURE 2 Logistic regression for IRC-confirmed objective response vs. ADC or MMAE cycle 1 AUC, cycle 1 C_{max}, and $C_{avgLast}$ (base model). This figure shows the logistic regression for IRC-confirmed objective response versus (a) ADC cycle 1 AUC, (b) ADC cycle 1 C_{max}, (c) ADC C_{avg} (base model), (d) MMAE cycle 1 AUC, (e) MMAE cycle 1 C_{max}, and (f) MMAE $C_{avgLast}$ (base model). The red solid line and green shaded area represent the logistic regression model prediction and 95% confidence interval of predictions. Points show exposure of individual patients who experienced events ($p=1$) and those who did not experience events ($p=0$) vertically jittered for better visualization. Black squares and vertical green lines show observed fraction of patients who experienced events in each exposure tertile and 95% confidence interval for these fractions. Dashed vertical lines show bounds of exposure tertiles. *P* value is provided by *glm()* function. ADC, antibody-drug conjugate; AE, adverse event; AUC, area under the concentration-time curve; C_{max}, maximum concentration; $C_{avgLast,}$ predicted average concentrations from time zero until end of the cycle in which an event occurred; IRC, independent review committee; MMAE, monomethyl auristatin E.

for the safe and effective use of TV. The TV-related ocular AEs are likely inflammatory and result in characteristic symptoms that are easily recognized by patients and healthcare providers. The probability of AEs of special interest of grade 2+ bleeding and peripheral neuropathy were not correlated with ADC or MMAE exposure over the observed period.

Tubulin inhibition is an increasingly important treatment strategy in oncology and has been investigated alone or in combination with other agents in the treatment of non–small cell lung cancer, melanoma, and sarcoma.[26,33] Compounds such as MMAE interfere with microtubule assembly, leading to cell cycle arrest and eventually cell death. In the present study, the probability of all SAEs significantly increased as MMAE cycle 1 AUC increased (Table 1). Payloads such as MMAE are highly cytotoxic, masked in the bloodstream by their conjugation into ADCs, and designed to convey their effects directly to targeted tumor cells.[26] Cells that have undergone MMAE-directed cell death may release unconjugated MMAE into the extracellular environment, or the ADC linker may be cleaved under specific conditions in the tumor microenvironment before internalization, contributing to MMAE-related bystander effects.[18,26] The significant, linear relationship between MMAE and all SAEs observed in the present study may be a result of MMAE inducing cytotoxic effects in nontumor cells through MMAE-mediated effector mechanisms, such as direct and bystander cytotoxicity, as well as the induction of immunogenic cell death.[17–19,21]

In terms of efficacy, the probability of response increased significantly as ADC exposure increased (cycle 1 C_{max}; Table 2). The DOR was not correlated with ADC

TABLE 3 PFS, OS, and DOR: Summary of CPH base models for ADC and MMAE.

Exposure	Exposure measure	β	SE	p Value	Model
ADC cycle 1 AUC	PFS	−0.019	0.009	0.028	Base
		−0.005	0.012	0.682	Full
	OS	−0.038	0.011	<0.0005[a]	Base
		−0.034	0.013	0.010[a]	Full
	DOR	0.016	0.029	0.576	NA
ADC cycle 1 C_{max}	PFS	−0.032	0.015	0.029	Base
		−0.015	0.019	0.430	Full
	OS	−0.053	0.018	0.003[a]	Base
		−0.044	0.022	0.044[a]	Full
	DOR	0.061	0.044	0.163	NA
ADC $C_{avgLast}$	PFS	0.044	0.206	0.832	Base
		0.093	0.250	0.711	Full
	OS	−0.368	0.231	0.111	Base
		−0.260	0.271	0.338	Full
	DOR	0.549	0.678	0.418	NA
MMAE cycle 1 AUC	PFS	0.014	0.005	0.005	Base
		0.012	0.007	0.063	Full
	OS	0.023	0.005	<0.0005[a]	Base
		0.023	0.007	0.001[a]	Full
	DOR	−0.032	0.024	0.183	NA
MMAE cycle 1 C_{max}	PFS	0.128	0.042	0.002	Base
		0.102	0.058	0.077	Full
	OS	0.190	0.040	<0.0005[a]	Base
		0.202	0.059	0.001[a]	Full
	DOR	−0.285	0.204	0.161	NA
MMAE cycle 1 C_{tr}	PFS	1.268	0.804	0.115	Base
		1.568	0.975	0.108	Full
	OS	1.816	0.753	0.016[a]	Base
		1.144	1.040	0.271	Full
	DOR	−2.492	3.668	0.497	NA
MMAE $C_{avgLast}$	PFS	0.393	0.101	<0.0005[a]	Base
		0.309	0.144	0.032[a]	Full
	OS	0.512	0.097	<0.0005[a]	Base
		0.509	0.149	0.001[a]	Full
	DOR	−0.564	0.512	0.271	NA

Note: A total of 8 baseline values for SUMDIAM were missing (6 patients from innovaTV 201; 1 from innovaTV 202; and 1 from innovaTV 204); data were imputed from the median values among patients with the same tumor type and non-missing SUMDIAM data.

Abbreviations: ADC, antibody-drug conjugate; AUC, area under the curve; β, estimate for exposure parameter; $C_{avgLast}$, predicted average concentrations from time zero until end of the cycle in which an event occurred; C_{max}, maximum concentration; CPH, Cox proportional hazard; C_{tr}, trough concentration; DOR, duration of response; MMAE, monomethyl auristatin E; NA, not applicable; OS, overall survival; PFS, progression-free survival; SE, standard error; SUMDIAM, individual sum of tumor diameters at baseline.

[a]Analyses associated with $p < 0.05$.

or MMAE exposure, and the probability of a PFS event significantly increased as MMAE $C_{avgLast}$ increased (Table 3). The risk of death significantly decreased as ADC cycle 1 AUC and cycle 1 C_{max} increased and significantly increased as MMAE cycle 1 AUC, cycle 1 C_{max}, and $C_{avgLast}$ increased (Table 3). The direct cytotoxicity

associated with TV might be negatively augmented by bystander cytotoxicity of adjacent cells and multiple immune-related effects.[17,19] Furthermore, the trend observed in the present study with MMAE exposures has been observed with other MMAE-based ADCs,[34,35] which may be due to some confounding factors that cannot be explained by covariates evaluated in the exposure-efficacy analyses.[36,37] For all significant exposure-efficacy relationships, the relationship with MMAE exposure was opposite from the relationship with ADC exposure even though there were no strong correlations between ADC exposure measures and MMAE exposure measures. Patients with poorer overall health tend to have a higher rate of AEs, lower response rate, and poorer prognosis. These patients are also prone to increased cachexia, which may lead to an increase in antibody catabolism, resulting in higher MMAE exposures.[37] Consistent with this hypothesis, in our analysis, MMAE exposure was higher in patients with poorer prognostic factors, including larger tumor size, lower albumin level, higher ECOG performance status, and hepatic impairment (data not shown). Drug-disease interactions have been reported for other biologic therapies, including trastuzumab, trastuzumab emtansine, and pembrolizumab, for which apparent exposure-efficacy relationships demonstrating lower efficacy in lower exposure quartiles may have been confounded by higher systemic clearances in patients with more advanced disease.[37–39] Therefore, interpretation of exposure and efficacy response analyses should consider potential confounding effects that baseline disease factors might have on the efficacy outcomes and on the PK of biologic therapeutics.[36]

Overall, the findings of the present study showed that there was an increase in the number of treatment-related AEs and an increase in efficacy as ADC cycle 1 exposure increased, similar to other MMAE-based ADCs.[27–29] The findings from the ER analyses support the clinical efficacy and safety data, suggesting that, of all the regimens evaluated to date, the proposed dose of TV 2 mg/kg q3w (up to 200 mg for patients ≥100 kg) provides a good balance between risk and benefit, with clinically important efficacy and a manageable safety profile.

AUTHOR CONTRIBUTIONS

C.P., J.V., L.G., R.G., W.D.H., H.W., and M.G. wrote the manuscript. C.P., J.V., L.G., R.G., L.N., I.S., W.D.H., H.W., and M.G. designed the research. L.G. performed the research. C.P., J.V., L.G., R.G., L.N., I.S., W.D.H., H.W., and M.G. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

L.G. is a paid consultant to Genmab A/S and Seagen Inc. C.P., I.S., and M.G. are employees of Genmab and may own stock. J.V., R.G., L.N., and W.D.H. are employees of Seagen Inc. and may own stock. H.W. was an employee at Seagen Inc. during development of this manuscript and is now an employee at Gilead Sciences, Inc.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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